Environ Health Perspect
DOI: 10.1289/EHP641

Supplemental Material

Perfluoroalkyl Substances during Pregnancy and Offspring Weight and Adiposity at Birth: Examining Mediation by Maternal Fasting Glucose in the Healthy Start Study

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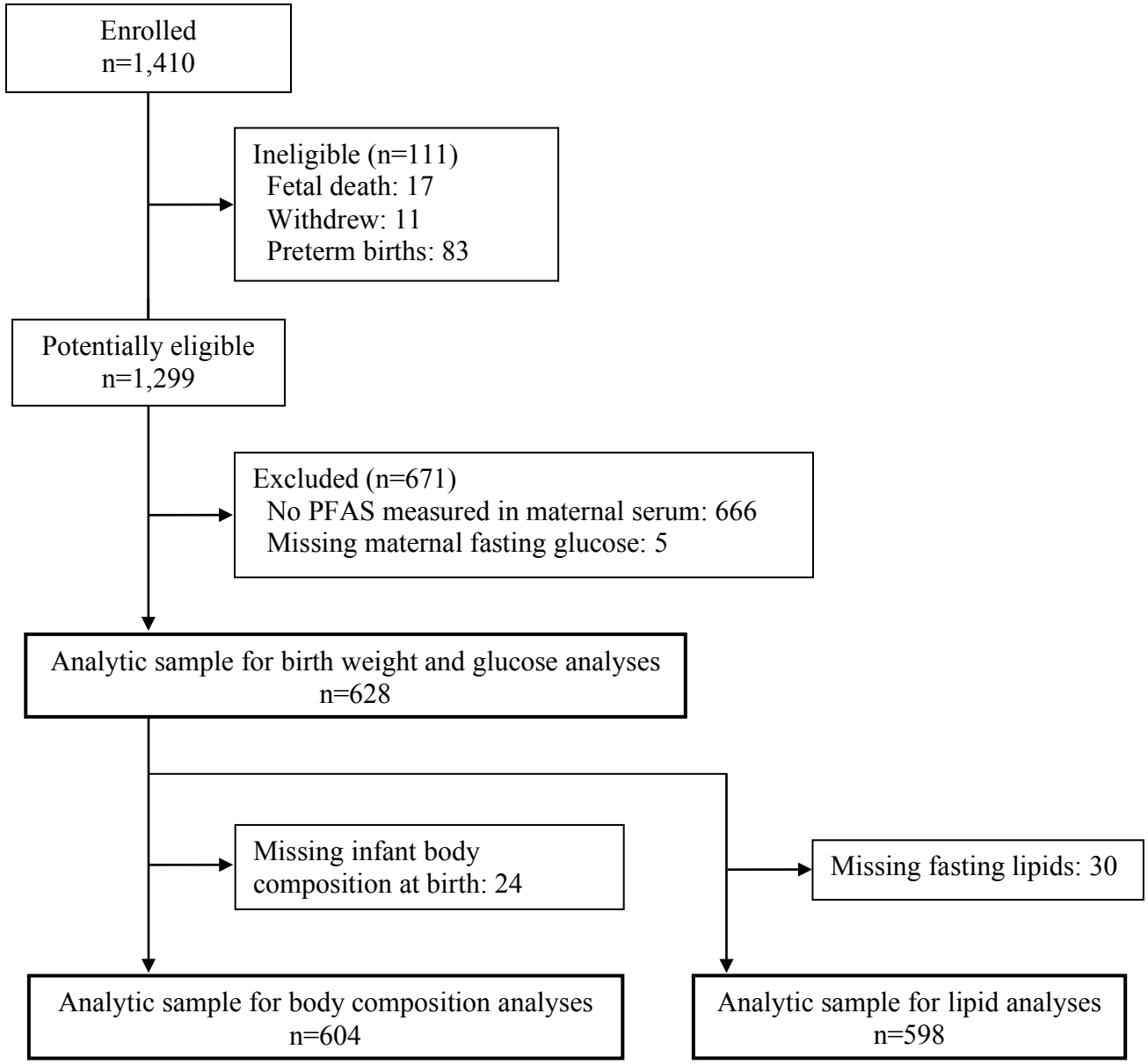

Figure S1. Participant eligibility flow chart.

Table S1. Characteristics of 1,299 mother-term infant pairs enrolled in the Healthy Start study, 2009-2014.

	Mean ± SD or n (%)
Age at delivery (years)	27.8 ± 6.2
16-19	158 (12)
20-24	263 (20)
25-29	320 (25)
30-34	373 (29)
35-39	161 (12)
40-45	24 (2)
Pre-pregnancy body mass index (kg/m^2)	25.7 ± 6.2
<18.5	40 (3)
18.5-24.9	672 (52)
25.0-29.9	324 (25)
≥30.0	261 (20)
Missing	2
Race/ethnicity (n, %)	
Non-Hispanic white	705 (54)
Hispanic	324 (25)
Non-Hispanic black	191 (15)
All others	79 (6)
Education (n, %)	
Less than 12^{th} grade	184 (14)
High school degree or equivalent	241 (19)
Some college or associate's	299 (23)
Four year college (bachelor's)	289 (22)
Graduate degree	286 (22)
Household income (n, %)	
$20,000 or less	194 (15)
$20,001 to $40,000	178 (14)
$40,001 to $70,000	242 (19)
$70,001 or more	428 (33)
Don't know	257 (20)
Any previous pregnancies (n, %)	840 (65)
Any smoking during pregnancy (n, %)	112 (9)
Gestational weight gain (kg)	13.7 ± 7.4
Cesarean delivery (n, %)	259 (21)
Female infant (n, %)	603 (48)
Gestational age at birth (days)	277 ± 8
Birth weight (g)	3276 ± 441
Adiposity at birth (% fat mass)[a]	9.1 ± 3.9

[a] 271 infants did not have adiposity measured within 3 days of birth.

Table S2. Concentrations (ng/ml) of 11 perfluoroalkyl and polyfluoroalkyl substances among 628 eligible participants in the Healthy Start study.

				Percentiles				
	Abbreviation	Percent detected	LOD	5th	25th	50th	75th	95th
Perfluorooctane sulfonamide	PFOSA	0	0.1	<LOD	<LOD	<LOD	<LOD	<LOD
2-(N-ethyl-perfluorooctane sulfonamido) Acetate	Et-PFOSA-ACOH	1	0.1	<LOD	<LOD	<LOD	<LOD	<LOD
2-(N-methyl-perfluorooctane sulfonamido) acetate	Me-PFOSA-ACOH2	29	0.1	<LOD	<LOD	<LOD	0.1	0.4
Perfluorohexane sulfonate	PFHxS	99	0.1	0.2	0.5	0.8	1.2	2.8
n-perfluorooctanoate	n-PFOA	100	0.1	0.3	0.7	1.1	1.6	2.7
Branched perfluorooctanoates	Sb-PFOA	5	0.1	<LOD	<LOD	<LOD	<LOD	0.1
Perfluorodecanoate	PFDeA	65	0.1	<LOD	<LOD	0.1	0.2	0.4
n-perfluorooctane sulfonate	n-PFOS	99	0.1	0.5	1.1	1.8	2.8	4.9
Perfluoromethylheptane sulfonates	Sm-PFOS	97	0.1	0.2	0.3	0.6	1.0	1.8
Perfluorodimethylhexane sulfonates	Sm2-PFOS	1	0.1	<LOD	<LOD	<LOD	<LOD	<LOD
Perfluorononanoate	PFNA	98	0.1	0.2	0.3	0.4	0.6	1.1

Table S3. Spearman rank correlations of serum concentrations (ng/ml) of perfluoroalkyl substances among 628 eligible participants in the Healthy Start study.

	PFOA	PFOS	PFNA	PFDeA	PFHxS
PFOA*	1	0.68	0.76	0.56	0.61
PFOS*		1	0.62	0.49	0.65
PFNA			1	0.65	0.45
PFDeA				1	0.27
PFHxS					1

Abbreviations: PFDeA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.

Table S4. Maternal serum perfluoroalkyl substances and neonatal fat mass and fat-free mass among 604 mother-infant pairs in the Healthy Start study.

	Unadjusted change in fat mass (g) and 95% CI	Adjusted[a] change in fat mass (g) and 95% CI	Unadjusted change in fat free mass (g) and 95% CI	Adjusted[a] change in fat free mass (g) and 95% CI
PFOA (ng/ml)[b]	-11.40 (-28.87, 6.08)	-21.83 (-39.73, -3.93)	2.27 (-36.74, 41.29)	-23.97 (-59.74, 11.81)
0.1-0.8	Ref	Ref	Ref	Ref
0.9-1.4	-6.11 (-34.52, 22.29)	-14.24 (-41.45, 12.97)	24.19 (-39.27, 87.64)	1.18 (-53.38, 55.74)
1.4-17.0	-24.26 (-52.67, 4.15)	-44.82 (-73.87, -15.78)	2.25 (-61.21, 65.70)	-31.81 (-90.06, 26.44)
PFOS (ng/ml)[b]	0.00 (-15.83, 15.84)	-1.28 (-16.93, 14.38)	4.83 (-30.48, 40.14)	-6.91 (-38.09, 24.27)
<LOD-1.8	Ref	Ref	Ref	Ref
1.8-3.2	6.78 (-22.13, 35.68)	2.90 (-24.28, 30.07)	-2.20 (-66.75, 62.35)	-27.36 (-81.59, 26.88)
3.2-15.6	-15.73 (-44.14, 12.67)	-22.72 (-50.87, 5.43)	-20.76 (-84.19, 42.68)	-33.58 (-89.77, 22.61)
PFNA (ng/ml)[b]	-11.75 (-30.39, 6.89)	-18.95 (-37.23, -0.67)	3.16 (-38.45, 44.77)	-31.55 (-68.00, 4.90)
<LOD-0.4	Ref	Ref	Ref	Ref
0.5-6.0	-30.07 (-53.84, -6.30)	-37.99 (-61.09, -14.88)	-10.63 (-63.88, 42.62)	-45.15 (-91.43, 1.13)
PFDeA (ng/ml)[b]	2.37 (-17.51, 22.25)	1.97 (-17.19, 21.14)	18.18 (-26.14, 62.49)	11.20 (-26.96, 49.36)
≤0.1	Ref	Ref	Ref	Ref
0.2-3.5	-1.83 (-25.88, 22.21)	-3.77 (-26.89, 19.35)	14.96 (-38.64, 68.56)	9.43 (-36.61, 55.48)
PFHxS (ng/ml)[b]	-8.59 (-22.94, 5.77)	-12.31 (-26.76, 2.14)	18.12 (-13.89, 50.13)	3.54 (-25.31, 32.38)
<LOD-0.5	Ref	Ref	Ref	Ref
0.6-1.0	18.08 (-10.05, 46.22)	6.13 (-20.81, 33.06)	67.68 (4.61, 130.74)	34.58 (-19.47, 88.62)
1.1-10.9	-29.97 (-58.68, -1.26)	-37.01 (-65.92, -8.09)	29.85 (-34.51, 94.20)	7.67 (-50.35, 65.69)

Abbreviations: CI, confidence interval; PFDeA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate. LOD, limit of detection. LOD was 0.1 ng/ml for all PFAS.

[a] Adjusted for maternal age, pre-pregnancy body mass index, race/ethnicity, education, gestational weight gain, smoking, gravidity, gestational age at blood draw, infant sex, and gestational age at birth.

[b] Beta-coefficients per natural-log unit increase in each perfluoroalkyl substance, and for upper categories compared to the lowest.

Table S5. Maternal serum perfluoroalkyl substances and fasting lipids at mid-pregnancy among 598 mother-infant pairs[a] in the Healthy Start study.

	Unadjusted change in HDL (mg/dl) and 95% CI	Adjusted[b] change in HDL (mg/dl) and 95% CI	Unadjusted change in ln-triglycerides (ln-mg/dl) and 95% CI	Adjusted[b] change in ln-triglycerides (ln-mg/dl) and 95% CI
PFOA (ng/ml)[c]	2.69 (1.09, 4.29)	1.90 (0.22, 3.59)	-0.010 (-0.052, 0.032)	-0.006 (-0.049, 0.036)
0.1-0.8	Ref	Ref	Ref	Ref
0.9-1.4	1.85 (-0.76, 4.46)	1.71 (-0.87, 4.29)	0.032 (-0.036, 0.100)	0.007 (-0.058, 0.072)
1.4-17.0	3.09 (0.48, 5.71)	1.72 (-1.02, 4.46)	-0.021 (-0.089, 0.047)	-0.020 (-0.089, 0.049)
PFOS (ng/ml)[c]	1.77 (0.32, 3.22)	0.79 (-0.68, 2.27)	-0.023 (-0.060, 0.015)	0.004 (-0.033, 0.041)
<LOD-1.8	Ref	Ref	Ref	Ref
1.8-3.2	2.16 (-0.49, 4.81)	1.49 (-1.08, 4.05)	-0.012 (-0.080, 0.057)	0.009 (-0.056, 0.073)
3.2-15.6	2.22 (-0.39, 4.83)	0.60 (-2.06, 3.26)	-0.076 (-0.144, -0.009)	-0.042 (-0.109, 0.025)
PFNA (ng/ml)[c]	2.15 (0.43, 3.88)	0.97 (-0.77, 2.71)	-0.005 (-0.050, 0.040)	-0.005 (-0.048, 0.039)
<LOD-0.4	Ref	Ref	Ref	Ref
0.5-6.0	1.89 (-0.29, 4.07)	0.29 (-1.89, 2.48)	0.009 (-0.048, 0.066)	0.016 (-0.039, 0.071)
PFDeA (ng/ml)[c]	1.59 (-0.23, 3.40)	0.21 (-1.59, 2.00)	-0.020 (-0.067, 0.027)	-0.002 (-0.048, 0.043)
≤0.1	Ref	Ref	Ref	Ref
0.2-3.5	1.60 (-0.60, 3.80)	-0.01 (-2.18, 2.15)	-0.013 (-0.071, 0.044)	0.007 (-0.047, 0.062)
PFHxS (ng/ml)[c]	2.09 (0.78, 3.39)	1.60 (0.25, 2.96)	-0.043 (-0.077, -0.009)	-0.032 (-0.066, 0.002)
<LOD-0.5	Ref	Ref	Ref	Ref
0.6-1.0	1.60 (-1.01, 4.21)	1.72 (-0.83, 4.28)	-0.016 (-0.083, 0.052)	0.010 (-0.054, 0.074)
1.1-10.9	2.92 (0.27, 5.57)	2.06 (-0.67, 4.79)	-0.120 (-0.188, -0.052)	-0.089 (-0.157, -0.021)

Abbreviations: CI, confidence interval; PFDeA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate. LOD, limit of detection. LOD was 0.1 ng/ml for all PFAS.

[a] 30 participants excluded due to missing lipid measures.

[b] Adjusted for maternal age, race/ethnicity, pre-pregnancy body mass index, education, gravidity, smoking, and gestational age at blood draw.

[c] Beta-coefficients per natural-log unit increase in each perfluoroalkyl substance, and for the upper categories versus the lowest.

Table S6. Natural direct effects and indirect effects mediated through maternal glucose concentration among 628 mother-infant pairs in the Healthy Start study.

Exposure and outcome	Effect estimated	Estimate and 95% confidence interval
Continuous ln-PFOA and birth weight	Natural direct effect	-49.87 (-94.54, -5.20)
	Natural indirect effect	-1.54 (-7.04, 3.95)
	Total effect	-51.42 (-95.64, -7.19)
Continuous ln-PFNA and birth weight	Natural direct effect	-56.20 (-101.81, -10.58)
	Natural indirect effect	-1.42 (-6.52, 3.68)
	Total effect	-57.62 (-102.80, -12.43)
Highest versus lowest tertile of PFOA and adiposity	Natural direct effect	-0.88 (-1.65, -0.11)
	Natural indirect effect	-0.09 (-0.20, 0.02)
	Total effect	-0.97 (-1.74, -0.20)
Above versus at or below median PFNA and adiposity	Natural direct effect	-0.75 (-1.38, -0.13)
	Natural indirect effect	-0.10 (-0.20, 0.00)
	Total effect	-0.85 (-1.47, -0.23)
Highest versus lowest tertile of PFHxS and adiposity	Natural direct effect	-0.89 (-1.60, -0.17)
	Natural indirect effect	-0.10 (-0.22, 0.01)
	Total effect	-0.99 (-1.71, -0.27)

Abbreviations: PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate.

Table S7. Comparison of least squares and elastic net regression multi-pollutant models for the association between perfluoroalkyl substances and birth weight and adiposity among mother-infant pairs[a] in the Healthy Start study.

	Birth weight (g)			Adiposity at birth (%)		
	Least squares estimate and 95% confidence interval[b]	Variance inflation in least squares model	Penalized elastic net estimate[c]	Least squares estimate and 95% confidence interval[b]	Variance inflation in least squares model	Penalized elastic net estimate[d]
PFOA	-69.66 (-148.19, 8.87)	3.64	-14.47	-0.68 (-1.50, 0.14)	3.74	-0.18
PFOS	29.09 (-32.56, 90.75)	2.75	Not selected	0.91 (0.27, 1.55)	2.78	0.02
PFNA	-92.43 (-167.21, -17.64)	2.92	-32.65	-0.63 (-1.42, 0.16)	3.08	-0.02
PFDeA	97.52 (31.45, 163.59)	2.02	15.73	0.54 (-0.15, 1.24)	2.08	Not selected
PFHxS	11.49 (-38.89, 61.87)	2.23	Not selected	-0.45 (-0.97, 0.07)	2.21	-0.08

Abbreviations: PFDeA, perfluorodecanoate; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoate; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate.

[a] Birth weight, n=628; adiposity, n=604.

[b] Estimated beta-coefficients per natural-log unit increase in each chemical, adjusted for other chemicals, maternal age, pre-pregnancy BMI, race/ethnicity, education, gestational weight gain, smoking, gravidity, gestational age at blood draw, infant sex, gestational age at birth.

[c] Adjusted for selected chemicals, gestational age at birth, non-Hispanic black race/ethnicity, infant sex, gestational weight gain, maternal age, pre-pregnancy BMI, gravidity, smoking, other race/ethnicity, gestational age at blood draw.

[d] Adjusted for selected chemicals, infant sex, pre-pregnancy BMI, gestational age at birth, gestational weight gain, non-Hispanic white race/ethnicity, gestational age at blood draw, gravidity, maternal age.